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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,160	08/09/2001	Sushma Pati	A-64580-4/RFT/RMS/AMS	4009

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EXAMINER	
FALK, ANNE MARIE	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,160	PATI ET AL.	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-37 and 41-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-37 and 41-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 August 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *02/03,03/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed March 9, 2004 has been entered. Claims 38-40 and 71 have been cancelled.

Applicants' election without traverse of Group V, Claims 32-37 and 41-70 in the response filed March 9, 2004 is acknowledged. The elected invention is drawn to a method of making a transgenic mammal comprising a modified endogenous nucleic acid, wherein the preselected target DNA sequence encodes an enzyme. In view of the Election of Species requirement, Applicants further elected a gene encoding a human enzyme.

Claims 32-37 and 41-70 are pending in the instant application.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 32-37 and 41-70 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims cover a method of making a germ-line modified human, which is non-statutory subject matter. Inclusion of the phrase "non-human" would be remedial.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 32-37 and 41-70 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification fails to provide an enabling disclosure for the claimed method of making a transgenic mammal because the specification does not teach specific phenotypic alterationa as a result of the various genetic modifications contemplated. The claimed invention is drawn to methods of making transgenic mammals with no particular phenotype, wherein any endogenous gene encoding an ion-channel protein, a G-protein coupled receptor, an immunoglobulin, a growth factor, an enzyme, or a milk protein, or various other products, is modified in any way. Because the specification discloses no phenotype for the genetically modified mammals, undue experimentation would have been required for one of skill in the art to make and use the claimed invention, as a method of making a product has use only if the product made has use. Given that the phenotype of a transgenic animal or genetically modified animal cannot be predicted and given that only mice with a single point mutation in the gene encoding ornithine carbamoyltransferase have been prepared, one of skill in the art would have been required to exercise undue experimentation to practice the claimed method to make and use any of the other claimed genetically modified mammals.

The specification fails to provide an enabling disclosure for making any type of genetic modification because the only method contemplated for making such genetically modified animals is not enabled for inserting entire genes into specifically selected sites of the target genome. The specification demonstrates that recA-mediated gene targeting can be used to make single base substitutions using recA-coated targeting polynucleotides. However, the specification also discloses that as the region of heterology increases, the stability of four-strand hybrids decreases significantly. Thus, the efficiency of recombination would be expected to be much lower for larger deletions or insertions. While the specification enables single base substitutions, no guidance is provided for making other types of changes to the genome.

The specification teaches a method of making transgenic mice using a recA-mediated gene targeting strategy. While the specification contemplates the use of the method to make targeted changes to the genome of other mammals, an enabling disclosure is not provided. The specification fails to provide an enabling disclosure for making targeted changes to any mammal other than the mouse because pronuclear microinjection of zygotes typically results in the random integration of the exogenously introduced DNA into the genome of the host and recA-catalyzed gene targeting has not been shown to be as efficient as random integration in any species other than the mouse. Because the efficiency of integration into the genome varies significantly from species to species (see below), one skilled in the art would have been required to exercise undue experimentation in order to practice the claimed method of making the various genetic modifications recited in the claims in any species other than the mouse.

The specification does not contain a written description of genetically modified animals of the type claimed. No particular phenotype is disclosed for the genetically modified animals other than the anticipated expression or inactivation of the modified gene. There is no demonstration that the claimed animals would in fact express the modified genes from the various modified forms contemplated by the claims.

The specification fails to provide an enabling disclosure for the method of making any species of genetically modified mammal harboring alleles of the type claimed because the guidance offered in the specification is not sufficient to teach one of skill in the art how to prepare the claimed genetically modified mammals exhibiting a phenotypic alteration that results from the genetic modification. The mere capability to perform gene transfer in various species is not enabling for the claimed methods because the desired phenotype cannot be predictably achieved by simply introducing any construct into the genome. While gene transfer techniques are well-developed for a number of species, including the mouse, methods for achieving the desired level of gene expression in appropriate tissues are less well-

established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. While the recA-mediated gene targeting method disclosed in the specification relies on site-specific recombination, random integration can also occur and methods for preventing or detecting random integration events are not disclosed. Methods for selecting the desired site-specific recombinant are not disclosed. Therefore, the disclosed method is accompanied by some of the same limitations associated with random integration methods. The resultant genetically modified mammals encompass transgenic mammals generated by random integration of exogenous DNA into the genome. Insertional inactivation of endogenous genes and position effects (see Wall, 1996, p. 61, paragraph 3) can dramatically influence the phenotype of the resultant transgenic animal. Integration of the transgene near highly active genes or, alternatively, in a transcriptionally inactive region, can influence its level of expression. Furthermore, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depends on the particular gene construct used, to an unpredictable extent. The particular genetic elements required for appropriate expression varies from species to species. Thus, a construct that confers the desired phenotype in a mouse cannot necessarily achieve the same result in a rat. Wall (1996) reports that our lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior (p. 61, paragraph 3). This is especially relevant for species in which genetic studies are less advanced than in the mouse. Thus, the species-specific requirements for transgene design introduces an additional level of unpredictability associated with the development of transgenic animals. Furthermore, transgene integration efficiency varies from species to species, ranging from 1% in farm animals (cattle, sheep, and pigs) to about 3% in laboratory animals (mice, rabbits, and rats) as reported by Wall (p. 61, paragraph 2). Thus, in the absence of any working examples, the existence of any phenotypic alteration resulting from

the genetic modifications of the type claimed in any species of mammal, is highly unpredictable. Given the lack of working examples and the unpredictability in the art, one of ordinary skill in the art would have been required to engage in undue experimentation in order to practice the claimed methods and use the product produced by the method (i.e., the transgenic mammals).

While the species-specific requirements for transgene design are not clearly understood, examples in the literature demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al., 1990 produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al., 1990 describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human β_2-microglobulin transgenes. Both investigations were preceded by the failure to develop human disease-like symptoms in transgenic mice (Mullins et al., 1989; Taurog et al., 1988) expressing the same transgenes that successfully caused the desired symptoms in transgenic rats.

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to practice the full scope of the claimed method and how to use the products produced thereby without undue experimentation. The claims cover methods of making any mammal with any modification in an endogenous gene, but the specification does not enable any modification, other than a single point mutation, in any species, other than the mouse. In the absence of disclosure of genetically modified mammals fully representative of the genetic modifications claimed in the species claimed, and exhibiting an appropriate phenotype, undue experimentation would have been required to practice the claimed invention.

Accordingly, given the demonstrated lack of predictability in the art, the limited amount of guidance given in the specification, the state of the prior art, the quantity of experimentation needed, and the lack of applicable working examples, one of skill in the art would not be able to practice the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 32-37 and 41-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 32-37 and 41-70 are indefinite in their recitation of "a method of making a transgenic mammal" in the preamble of the claim because the steps recited in the body of the claim result only in the production of a pregnant female and do not result in the production of a transgenic mammal. Thus, the body of the claim is in conflict with the preamble.

Claims 32-37 and 41-70 are indefinite with regard to the "modified endogenous nucleic acid" because it is unclear relative to what standard or point of reference the endogenous nucleic acid is considered to be "modified." Furthermore, it is unclear what would be regarded as an "endogenous nucleic acid." For example, the term could be limited to the genes present in any given individual of the species under consideration, thereby encompassing mutant forms of genes not present in other individuals. At the same time, the gene present in the given individual may have, at one point, been derived from an exogenous source, e.g. a virus. Alternatively, the term could be understood to refer to any form/allele of any gene within the pool of genes of that species, encompassing genes and mutant forms of genes not present in every individual of the species.

Claims 34 and 65 are indefinite in the recitation of "farm" mammal because it is unclear what would be encompassed by this term. More precise inherent characteristics of the animals must be indicated to identify any particular class or group of animals. The metes and bounds of the claim are not clearly set forth.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 10:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on (571) 272-0804. The central official fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to Dianiece Jacobs, whose telephone number is (571) 272-0532.

Anne-Marie Falk, Ph.D.

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER